REMARKS

Applicants have cancelled claims 6 and 7 without prejudice to continued prosecution, and have amended claims 1, 5, 8, 9, 12, and 14. The amended claims find support in the claims as originally filed. Accordingly, no new matter has been added. In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 1-5 and 8-14.

Objections

The Examiner objected to the specification because the sequences set forth on page 13 lack SEQ ID NO identifiers. Applicants have amended the specification to set forth the appropriate sequence identifiers, and enclose a paper copy and computer readable form of the sequence listing. No new matter has been added. The specification is in compliance with the requirements for patent applications containing nucleotide and amino acid sequences. Accordingly, Applicants respectfully request withdrawal of the objection to the specification.

Rejections under 35 U.S.C. § 102(a)

The Examiner rejected claims 1-14 under 35 U.S.C. § 102(a) as anticipated by Kong *et al.*, WO 01/61039 A2, published August 23, 2001. Specifically, the Examiner stated that Kong *et al.* teach a method for predicting patient responsiveness to a 5-HT3 receptor antagonist comprising determining the genotype of the patient's 5-HTTP gene and correlating the genotype with the patient's responsiveness. The Examiner stated that Kong *et al.* teach alosetron as one 5-HT3 receptor antagonist used in the treatment for diarrhea-predominant irritable bowel syndrome, and that Kong *et al.* teach "amplifying a nucleic acid comprising the promoter region of the patient's 5-HTTP gene in order to obtain an amplified product and determining the size of the amplified product to identify a long variant/long variant genotype with patient responsiveness." The Examiner stated that Kong *et al.* teach that "the long variant/long variant genotype is related to a greater patient responsiveness than the short variant/long variant genotype," that the "patient responsiveness is determined by measuring a patient parameter," and that "patient responsiveness is determined by comparing a measured negative net change in the geometric center of colonic transit of at least 1.14 colonic regions after treatment with the 5-HT3

receptor antagonist." The Examiner also noted that Kong *et al.* teach "a method for treating a patient with diarrhea-predominant IBS comprising obtaining a biological sample from the patient, genotyping the promoter region of the patient's 5-HTTP gene, and administering a 5-HT3 receptor antagonist to patients having a long variant/long variant genotype in the promoter region." Finally, the Examiner stated that Kong et al. teach "a method for identifying a patient population for inclusion in a 5-HT3 receptor antagonist clinical trial comprising obtaining a biological sample from a potential participant, genotyping the promoter region of the 5-HTTP gene contained within the biological sample, and identifying the potential participant as suitable for inclusion based on the potential participant's having the long variant/long variant genotype." In sum, the Examiner rejected all claims as anticipated under 35 U.S.C. § 102(a).

Applicants respectfully disagree. Claims 1-5 and 8-11, as amended, recite a method for predicting patient responsiveness to a 5-HT3 receptor antagonist that includes determining a genotype of the promoter region of the patient's serotonin transporter protein gene, where the genotype is selected from the group consisting of a long variant/long variant, short variant/long variant, and short variant/short variant; and correlating the long variant/long variant genotype with a greater patient responsiveness to the 5-HT3 receptor antagonist. Similarly, present claims 12 and 13, as amended, recite a method for treating a patient with diarrhea-predominant irritable bowel syndrome. The method includes obtaining a biological sample from the patient, genotyping the promoter region of the serotonin transporter protein gene in the biological sample obtained from the patient, and administering to the patient an effective amount of a 5-HT3 receptor antagonist if the patient has a long variant/long variant genotype in the promoter region of the serotonin transporter protein gene. Finally, claim 14, as amended, recites a method for identifying a patient population for inclusion in a 5-HT3 receptor antagonist clinical trial. The method includes obtaining a biological sample from a potential participant in the clinical trial; genotyping the promoter region of the serotonin transporter protein gene contained within the biological sample; and identifying the potential participant as suitable for inclusion in the patient population based on the presence of a long variant/long variant genotype in the promoter region of the potential participant's serotonin transporter protein gene.

At no point does the Kong *et al.* reference disclose, teach, or suggest such methods. Contrary to the Examiner's assertions, nowhere in the Kong *et al.* reference is greater patient

responsiveness to 5-HT3 receptor antagonists, or inclusion in a patient population for a 5-HT3 receptor antagonist clinical trial, or treatment of IBS with a 5-HT3 receptor antagonist, correlated with, or based on the presence of, a long variant/long variant genotype. In fact, the Kong *et al.* reference specifically discloses that a deletion/deletion genotype ("del/del"), which corresponds to the present short variant/short variant genotype, demonstrated an "increased incidence in favorable therapeutic response" to alosetron treatment in a clinical trial setting, with higher incidence of relief of IBS symptoms, as compared to subjects with short variant/long variant ("del/ins") and long variant/long variant ("ins/ins") genotypes. See Kong *et al.*, Example 2, page 21. Thus, the Kong *et al.* reference does not anticipate claims 1-5 and 8-14. In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1-5 and 8-14 under 35 U.S.C. § 102(a).

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1, 5, 12 and 14 as indefinite under 35 U.S.C. § 112, second paragraph, because of the abbreviation "5-HTTP" in the claims. Specifically, the Examiner commented that it was unclear as to whether the abbreviation "5-HTTP" referred to the serotonin transporter gene or serotonin transporter linked polymorphic gene region. Applicants have herein amended claims 1, 5, 12, and 14 to recite "serotonin transporter protein" in place of the abbreviation "5-HTTP." Support for such an amendment may be found at, e.g., page 2, lines 6-8 of the specification. Accordingly, Applicants respectfully request withdrawal of the rejections of claims 1, 5, 12, and 14 under 35 U.S.C. § 112, second paragraph.

The Examiner rejected claim 12 as indefinite under 35 U.S.C. § 112, second paragraph. In particular, the Examiner stated that the term "effective" in the claim was not defined by the claim, the specification did not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Examiner concluded that the metes and bounds of the claim could not be established because several parameters determined "effective" and because no single set of conditions was recognized by the art as being "effective" to the exclusion of all other conditions.

Applicants respectfully disagree. The proper test for determining whether the phrase "effective amount" is definite is whether one of skill in the art could determine specific values

for the amount based on the disclosure. See In re Mattison, 509 F.2d 563, 184 USPQ (CCPA 1975), and MPEP § 2173.05(c)(III). Furthermore, the phrase "effective amount" may be definite when read in the light of the specification, e.g., if the specification provides guidelines as to intended utilities. Id. The present specification sets forth specific values for dosages of 5-HT3 receptor antagonists at, e.g., page 9, lines 25-28. Furthermore, Applicants have noted in the specification that one intended utility of the 5-HT3 receptor antagonist is to treat diarrhea-predominant IBS. The effectiveness of such treatment may be measured by a patient parameter, e.g., by a net reduction in the geometric center of colonic transit post treatment. See Specification, page 9, lines 3-15. Accordingly, Applicants assert that the phrase "effective amount" is not indefinite, and respectfully request withdrawal of the rejection under § 112, second paragraph.

The Examiner rejected claim 12 under 35 U.S.C. § 112, second paragraph, because the term "sample's 5-HTTP gene" was confusing. In particular, the Examiner stated that it was unclear as to whether the term "sample's 5-HTTP gene" referred to a sample obtained from the patient or from another source. Applicants have herein amended claim 12 to recite "genotyping the promoter region of the serotonin transporter protein gene in said biological sample obtained from said patient." Accordingly, Applicants assert that the amended claim is sufficiently definite and respectfully request withdrawal of the rejection under § 112, second paragraph.

CONCLUSION

Applicants submit that claims 1-5 and 8-14 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned at the telephone number below if such will advance prosecution of this application. No fees are due as this response is being filed before the end of the shortened statutory period. The Commissioner is authorized to charge any fees or credit any overpayments to Deposit Account No. 06-1050.

Attached is a marked-up version of the changes being made by the current amendment.

Respectfully submitted,

Date: 11/27/02

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Version with markings to show changes made

In the specification:

Paragraph beginning at page 13, line 8 has been amended as follows:

Polymorphic regions in the 5-HTTP gene (GenBank Accession No. X76753) were amplified by polymerase chain reaction using the following primers:

5'-GGAGGAACTGACCCCTGAAAACTG-3' (SEQ ID NO: 1) and

5'-GCCGCTCTGAATGCCAGCAC-3' (SEQ ID NO: 2), which flank the 5-HTTP long polymorphic region and correspond with nucleotide positions 2219 to 2242 and 1671 to 1680 of the 5-HTTP gene, respectively.

In the claims:

Claims 6 and 7 have been cancelled.

Claims 1, 5, 8-9, 12, and 14 have been amended as follows:

1. (Once Amended) A method for predicting patient responsiveness to a 5-HT3 receptor antagonist, said method comprising:

(a) determining a genotype of the promoter region of said patient's serotonin transporter protein [5-HTTP] gene, said genotype selected from the group consisting of a long variant/long variant, short variant/long variant, and short variant/short variant; and

(b) correlating said long variant/long variant genotype with greater patient responsiveness to said 5-HT3 receptor antagonist.

5. (Once Amended) The method of claim 1, wherein said genotyping step comprises:

(a) amplifying a nucleic acid comprising the promoter region of said patient's serotonin transporter protein [5-HTTP] gene to obtain an amplified product; and

(b) determining the size of said amplified product to identify the [a] long variant/long variant, short variant/long variant, or short variant/short variant genotype of the promoter region of said patient's serotonin transporter protein [5-HTTP] gene.

8. (Once Amended) The method of claim 1 [6], wherein said greater patient responsiveness is determined by measuring a patient parameter.

9. (Once Amended) The method of claim 1 [6], wherein said greater patient responsiveness is determined by comparing a measured patient parameter with a pre-determined clinically significant threshold.

12. (Once Amended) A method for treating a patient with diarrhea-predominant irritable bowel syndrome comprising:

(a) obtaining a biological sample from said patient;

(b) genotyping the promoter region of the serotonin transporter protein [said sample's 5-HTTP] gene in said biological sample obtained from said patient; and

(c) administering to said patient an effective amount of a 5-HT3 receptor antagonist if said patient has a long variant/long variant genotype in the promoter region of the serotonin transporter protein [5-HTTP] gene.

14. (Once Amended) A method for identifying a patient population for inclusion in a 5-HT3 receptor antagonist clinical trial comprising:

(a) obtaining a biological sample from a potential participant in said clinical trial;

(b) genotyping the promoter region of the serotonin transporter protein [5-HTTP] gene contained within said biological sample; and

(c) identifying said potential participant as suitable for inclusion in said patient population based on the presence of a long variant/long variant genotype in the promoter region of said potential participant's serotonin transporter protein [5-HTTP] gene.